EXPERIMENTAL CAUSATION OF CONGENITAL DEFECTS AND ITS SIGNIFICANCE.

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Résumé.

Pendant ces dernières décades l'attention des auteurs a surtout été attirée sur la découverte des facteurs génétiques expliquant les malformations congénitales.

Cependant on a été amené à considérer que d'autres causes pouvaient expliquer ces anomalies et cette façon de voir a trouvé un regain d'intérêt quand on s'est aperçu de l'effet de certains facteurs septiques sur de semblables anomalies.

On s'est préoccupé, et à juste titre, des fautes de l'alimentation maternelle, particulièrement dans les déficiences en vitamines et des influences des différentes maladies de la mère sur le fœtus.

En 1943 l'auteur a eu son attention attirée sur les effets de l'insuline sur le développement d'anomalies du squelette des poules, alors qu'il étudiait le rôle du glycogène sur les cellules cartilagineuses.

Il a été injecté des doses d'insulines variées à des œufs de poule, à différents intervalles de leur incubation, ce qui a produit des déformations de la colonne vertébrale et des membres.

Les mêmes déformations du squelette ont été obtenues avec des injections de symthaline,

Des précautions techniques permettent d'exclure dans la genèse de ces troubles les blessures de l'embryon et celles des vaisseaux. D'ailleurs de quantités d'injections ont été faites avec de l'insuline suractivée et d'autres substances, sans provoquer la moindre difformité.

L'importance de l'action des injections d'insuline dépend de la date de celle-ci par rapport à l'incubation et de la quantité de produit injecté. Le pourcentage va de 46 à 85 %.

Cette conférence a été illustrée de nombreuses diapositives et d'un magnifique film en couleurs où l'on voit des poules atteintes de déformations des membres allant du pied-bot à la luxation congénitale.

During the past few decades the discovery of genetic factors leading to congenital malformations has attracted a great deal of attention whereas the importance of environ-

mental causes of **human** malformations has received relatively much less emphasis. However, the associations of developmental abnormalities such as cataract and cardiac spectal defects with epidemics of rubella demonstrates clearly that genetic factors cannot **always** be invoked as the cause of such abnormalities. The implication of this and other esually valuable epidemiological observations regarding mongolism and encephalo-ophtalmic dysplasia is that the broad principles wich govern the environmental disturbances of growth and differentiation in lower animals can also be applied with suitable modifications, to human malformations. In the human chief interest has centred around the possible effects that faults in maternel diets, especially vitamin deficiences, irradiation of the mother's pelciv organs, and various diseases of the mother may have upon the foetus.

I became interested in the insuline induced skeletal abnormalities in developing chick embryos as a result of an accidental observation I made in 1943 while I was investigating the role of glycogen granules in hypertrophic cartilage cells during endochondral ossification. I injected various doses of insulin into the yolks of hens' eggs at different intervals after the beginning of incubation (fig. 1) and noticed that some of the chicks showed X-ray appearances resembling osteogenesis imperfecta (osteopsathyrosis) inin the human that sime had developed spina bifida and other abnormalities of the spinal column, such as partial or complete suppression of the development of some vertebrae, while others showed deformities in the limbs. The technique of injection and the possible mode of action of insulin have already been described (Duraiswami P.K. British Medical Journal August 12, 1950, p. 384-394). Since then I have been able to induce similars deformities with « synthalin », certain sulphonamide compounds, and some thallium salts, and also induce « myodystrophy » sith 3 acetyl-pyridine.

I do not propose to enter here into a discussion on the histological, biochemical and other aspects of the problem but rather to give a brief summary of some of the observations wich have been made regarding insulin-induced abnormalities. I have used a simple apparatus not only for testing the fertility of an egg before injection into the yolk. In this way I have avoided injuring the embryo and chorionic

blood vessels. Lest anyone should think that the mere trauma of injection might induce deformities, I wish to make it clear that hundreds of control eggs have been injected using the same technique with physiological saline, « inactivated insuline », parathormone, calciferol and radioactive phosphorus, without any resulting deformities. I give only one injection of insuline into the yolk at a specified period after the beginning of incubation and no more, either during the remaining period of incubation or after hatching. The skeletal abnormalities have been listed in the accompagying table :

Insuline-induced Skeletal Abnormalities

Day of Injection after starting of incubation	Part of body **primarily** affected by insulin.
0-2^{d} day.	**Vertebral column.** Spina bifida; wedged vertebræ, scoliosis, non development of some vertebræ.
3rd day	**Feet.** Lobster claws; adduction deformities of claws resembling club-feet.
4th and 5th day.	**Limbs.** Tibial kyphosis; pseudarthrosis of tibia arthrogryposis.
6th day.	**Hip.** Congenital dislocation of the hip.
3rd to 6th days (high doses e.g. 3 to 6 units of insulin)	Generalised developmental disturbances of bone resembling « osteogenesis imperfecta » (osteopsathyrosis).

Within the range of 0.05 to 6 units of insulin I have injected, both the incidence and severity of the deformities seem to increase with the dose of the hormons, e.g. the occurence of limb deformities resulting from an injection of 2,5 units of insulin on the 5th day of incubation was 46 %, whereas with 5 units of insulin, injected also on the 5th day, it rose to 85 %. Spontaneous incidence of all types of limb deformities in chickens is 0,25 % according to Hutt and Greenwood (Hutt F.B. Greenwood A.W. Proccedings of the Royal Societe of Edinburgh, 1929, 49 p. 145) who examined 12.000 newly-hatched chicks. However, insulin-induced deformities can be prevented to a remarkable extent by injecting nicotinamide and riboflavin into eggs along with insulin.